REMARKS

Claims 2, 4, 16, 18, 21, 22 and 40 are currently under examination. Claim 40 is amended herein. Support for this amendment can be found in the specification on page 47, lines 19-26 and on page 48, lines 5-8. No new matter is believed to be added by this amendment. Pursuant to the following remarks, Applicants respectfully request allowance of the claims to issue.

Rejection Under 35 U.S.C. § 103(a)

The Office Action states that claims 1, 2, 4, 16, 18, 21, 22 and 40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Li et al. (US Patent No. 6,638,502) in view of Restifo et al. for reasons of record and additional reasons set forth in the Advisory Action dated June 13, 2007.

On page 2 of the Advisory Action, the Examiner has responded to Applicants' arguments by stating that Restifo et al. indicate the signal sequence may precede another peptide from 5 to 1000 amino acid residues (column 4, lines 32-40). The Advisory Action also states that prior art is presumed to be enabling, absent evidence to the contrary and that Applicants present no reasoning or evidence as to why expression of a heterologous polypeptide using the E19 signal sequence as taught by Restifo et al. would be unexpected. Further stated in the Advisory Action is that features upon which Applicants rely (i.e. increased circulating levels of an antiangiogenic protein and antiangiogenic activity) are not recited in the rejected claims (s). The Advisory Action also states that the E19 signal sequence directed expression and secretion of a heterologous protein for reasons made of record, i.e. the teachings of Restifo et al.

The Advisory Action further states that Li et al. teaches signal sequences (uPA and plasminogen, at the least, general sequences are disclosed in column 9, lines 44-53) to direct the secretion of antiangiogenic proteins (fragments of urokinase, angiostatin and endostatin, at the least) expressed from the adenoviral vectors. Furthermore, according to the Advisory Action, the systemic administration of an adenovirus expressing plasminogen (secreted by the plasminogen leader sequence) delivered high levels of the protein and prevented tumor establishment and growth (Griscelli et al. 1998, PNAS, see in particular page 6371, first column, first full ¶).

Also stated in the Advisory Action is that the secretion of angiostatin by the plasminogen signal sequence is considered the secretion of a heterologous protein, as the plasminogen signal sequence is not "naturally" associated with the angiostatin fragment. According to the Examiner, this is why the prior art teaches fusion proteins of a signal sequence linked to angiostatin. Furthermore, according to the Advisory Action a reading of the references allegedly reveals no teachings that a secretion signal must be "naturally" associated with the protein to be excreted. Rather, it is indicated that any signal sequence, in general may be used. See column 9, lines 44-53 of Li et al.

In response to the Examiner's objection that Applicants rely on features (i.e. increased circulating levels of an antiangiogenic protein and antiangiogenic activity) that are not recited in the rejected claims, claim 40 is amended herein to recite, "[a] compound comprising a recombinant nucleic acid encoding an antiangiogenic protein operatively linked to an adenovirus signal sequence inserted within a viral nucleic acid, wherein the recombinant nucleic acid can be packaged in a virus particle, wherein expression of the recombinant nucleic acid encoding the antiangiogenic protein results in production of the antiangiogenic protein, wherein the antiangiogenic protein targets endothelial cells, and wherein systemic delivery of the compound results in increased circulating levels of the antiangiogenic protein and inhibition of tumor growth."

In response to the Examiner's assertion that Restifo et al. indicates that a signal sequence may precede another peptide from 5 to 1000 amino acid residues, Applicants respectfully point out that setting forth a generic suggestion that an E19 signal sequence can drive expression and secretion of a peptide from 5 to 1000 amino acids does not provide any reasonable expectation that an E19 signal sequence could drive expression of a specific type of protein, i.e., an antiangiogenic protein that targets endothelial cells, that results in increased circulating levels of the antiangiogenic protein in order to achieve antiangiogenic activity via systemic administration, particularly when the only example set forth by Li et al. was a small peptide. In fact, since Restifo et al. is not a scientific publication, and because the claims issued in Restifo et al. do not include the cited range, there is no presumption that the scope of cited range has scientific validity for any protein other than E19 and a 9-mer peptide, much less the specific

types of proteins covered by the present claims. A reference is considered enabling if it includes a scientific basis for what it states. In this case, there is no such scientific basis, so a presumption of validity does not apply. The standard for obviousness is whether one of ordinary skill would have had a reasonable expectation of success. One of ordinary skill would be a peer in this scientific field. This unsupported assertion in Restifo et al. would not be considered by one of ordinary skill to provide a reasonable expectation for successfully expressing other proteins.

As further validation of these arguments, Applicants provide herewith as Exhibit 1, the Declaration of Dr. Renata Pasqualini, a Professor at The University of Texas M.D. Anderson Cancer Center (curriculum vitae attached hereto as Exhibit A), whereby Dr. Pasqualini declares that she has read and understood U.S. Patent No. 5,733,548 (Restifo et al.) and U.S. Patent No. 6,638,502 (Li et al.). She further declares that she is familiar with the research of Restifo et al., for example, as described in U.S. Patent No. 5,733,548 and the research of Li et al., for example, as described in U.S. Patent No. 6,638,502. It is Dr. Pasqualini's belief that although Restifo et al. discloses administration of P1A tumor peptide (SEQ ID NO: 6 (9 amino acids)) linked to an adenoviral E19 signal sequence in order to induce an immune response and Li et al. discloses intratumoral administration of an adenoviral vector that expresses angiostatin, one of skill in the art would not have considered utilizing the delivery system of Restifo et al. with the antiangiogenic protein of Li et al. in order to arrive at the claimed compositions of the instant application. The work of Restifo et al. showed only that the adenoviral E19 signal sequence could be used for expressing a small peptide in order to induce an immunogenic response. This is not closely related to a construct that expresses a full-sized protein that has anti-angiogenic function. Dr. Pasqualini further declares that although Restifo et al. makes the unsupported assertion that the E19 signal sequence can drive expression and secretion of a peptide from 5 to1000 amino acids in length, people of skill in the cancer therapy field did not view Restifo et al. as providing a reasonable expectation that an adenoviral E19 signal sequence could drive expression of an antiangiogenic protein that targets endothelial cells, and results in increased circulating levels of the antiangiogenic protein in order to treat tumors via systemic administration, particularly when the only example set forth by Restifo et al. is a small peptide.

In response to the Examiner's allegation that Li et al. clearly teaches a signal sequence to

direct the secretion of antiangiogenic proteins expressed from adenoviral vectors, Applicants respectfully point out that, as stated by the Examiner, the specific signal sequences utilized by Li et al. are a plasminogen signal sequence and a urokinase signal sequence, both of which are not adenoviral signal sequences. Furthermore, as declared by Dr. Renata Pasqualini, Li et al. disclose unrelated (not adenoviral) signal sequences to direct the secretion of antiangiogenic proteins expressed from adenoviral vectors. In fact, these signal sequences are sequences that are naturally associated with the antiangiogenic proteins being expressed by the vectors of Li et al. For example, the urokinase signal sequence is utilized to effect secretion of urokinase. In another example, the plasminogen signal sequence is utilized to effect secretion of an N-terminal fragment of human plasminogen. Li et al. teach only signal sequences that allow secretion of the polypeptide with which they are associated in nature (i.e. urokinase signal sequence and urokinase or plasminogen signal sequence and an N-terminal fragment of plasminogen). This teaching is conceptually distinct from and not suggestive of the idea that any signal sequence other than the signal sequence naturally associated with urokinase or plasminogen would result in the expression of these antiangiogenic molecules. Dr. Pasqualini further declares that it is even more surprising that a different signal sequence, for example, an adenoviral signal sequence, could be used to produce increased circulating levels of an antiangiogenic protein in order to treat tumors via systemic delivery as is shown in the present application.

With regard to the Examiner's assertion that general signal sequences are disclosed in column 9, lines 44-53, Applicants respectfully point out that Li et al. merely states that "[a] 'signal sequence' is included at the beginning of the coding sequence of a protein to be expressed on the surface of a cell. This sequence encodes a signal peptide, N-terminal to the mature polypeptide, that directs the host cell to translocate the polypeptide. The term 'translocation signal sequence' is used herein to refer to this sort of signal sequence. Translocation signal sequences can be found associated with a variety of proteins native to eukaryotes and prokaryotes, and are often functional in both types of organisms." This generic description provides no specific guidance as to what signal sequences can be used to express an antiangiogenic protein, much less drive expression of an antiangiogenic protein to increase circulating levels of the antiangiogenic protein and treat tumors via systemic delivery.

As stated above, the Examiner has cited Griscelli et al. as a reference showing that the systemic administration of an adenovirus expressing plasminogen (secreted by the plasminogen leader sequence) delivered high levels of protein and prevented tumor establishment and growth. Dr. Pasqualini has read and understood the Griscelli et al. reference and declares as follows: Similar to Li et al., Griscelli et al. teach an adenoviral vector that expresses the N-terminal fragment (amino acids 1-333) from human plasminogen operatively linked to the plasminogen signal sequence , i.e. the signal sequence that it is associated with in nature, and not an adenoviral signal sequence. The results obtained with the Griscelli et al. vector, wherein systemic administration of this vector resulted in decreased tumor establishment and growth, would not be considered to suggest the likelihood of a similar result when using an unrelated signal sequence, particularly a signal sequence not naturally associated with the expressed protein. Thus, one of skill in the art would not have thought to alter the vector of Griscelli et al. by utilizing an unrelated signal sequence, much less the adenoviral E19 signal sequence of Restifo et al. that was not naturally associated with any antiangiogenic protein and had only been utilized to secrete small peptides. This is because, there would have been no reasonable expectation that a nucleic acid encoding an antiangiogenic protein operatively linked to an adenoviral signal sequence would have worked at all, much less had properties that significantly advanced the practice of cancer therapy. There was no suggestion in the papers noted that the adenoviral E19 signal sequence-antiangiogenic protein construct would have the properties shown by Libutti et al.: 1) the ability to increase circulating levels of an antiangiogenic protein; and 2) the ability to treat tumors via systemic delivery.

As set forth above, the Advisory Action states that the secretion of angiostatin by the plasminogen signal sequence is considered the secretion of a heterologous protein, as the plasminogen signal sequence is not "naturally" associated with the angiostatin fragment. According to the Examiner, this is why the prior art teaches fusion proteins of a signal sequence linked to angiostatin. Furthermore, according to the Advisory Action a reading of the references allegedly reveals no teachings that a secretion signal must be "naturally" associated with the protein to be excreted. Rather, it is indicated that any signal sequence, in general may be used. See column 9, lines 44-53 of Li et al.

Applicants respectfully disagree and point out that both Li et al. and Griscelli et al. express an N-terminal fragment of plasminogen that expresses the first three kringle domains of plasminogen (up to residue 333; see Li et al. col. 26, lines 54-55, and Griscelli et al., page 6368, col. 1, first full ¶), i.e. angiostatin K3. Therefore, the plasminogen signal sequence is used to drive expression of a sequence with which it is naturally operatively linked, i.e. the first 333 amino acid residues of plasminogen. In other words, the plasminogen signal sequence is normally found linked to at least the first 333 residues of plasminogen. Therefore, these sequences are naturally associated. In fact, Applicants reiterate that the only specific examples of signal sequences utilized by Li et al. for local delivery are signal sequences that are naturally associated with the antiangiogenic sequences being expressed. Therefore, although the Examiner states that the references reveal no teachings that a secretion signal must be "naturally" associated with the protein to be excreted, given that Li et al. only disclose these examples for local delivery and make generic reference to other signal sequences, one of skill in the art would not reasonably expect that any other signal sequence, much less an adenoviral signal sequence would allow systemic delivery of an antiangiogenic protein to successfully treat tumors.

In further support of the nonbviousness of the claimed invention, Dr. Pasqualini declares that the results obtained by Libutti et al. with the claimed compositions have been lauded by others in the field as promising in the face of conflicting results with other anti-angiogenic therapies. For example, Dr. Judah Folkman, a renowned cancer researcher, when commenting on the paradoxical behavior of endostatin, noted that "...a gene therapy experiment by Andrew Feldman and Steven Libutti at NCI did produce some promising results. Feldman and Libutti transplanted an endostatin gene into mouse liver tumor cells and implanted the cells into mice. As they reported in the *Journal of the National Cancer Institute* last year, the implants expressing the highest amounts of endostatin were most strongly inhibited from growing." (See Exhibit B, "Setbacks for Endostatin," *Science* 295:2198-2199 (2002)) In this reference, the mouse liver tumor cells were transduced with a construct comprising a recombinant nucleic acid encoding an antiangiogenic protein, i.e. endostatin, operatively linked to an adenovirus signal sequence inserted within a viral nucleic acid, i.e. a retroviral nucleic acid (See Exhibit C, Feldman et al. "Effects of Retroviral Endostatin Gene Transfer on Subcutaneous and Intraperitoneal Growth of Murine Tumors" *Journal of the National Cancer Institute* 93(13):

1014-1020 (2001)). Therefore, in addition to treating tumors systemically, the claimed compositions have the ability to treat tumors via *ex vivo* transduction of tumor cells.

Dr. Pasqualini further declares that until the development of the claimed construct, nobody had been able to successfully treat tumors in both the systemic and implantation contexts. Furthermore, the circulating levels of endostatin achieved by Dr. Libutti were unprecedented, thus providing for the first time, evidence that a host can be utilized as a factory for production of sufficiently increased levels of an antiangiogenic polypeptide to effectively treat cancer patients. Therefore, it is my belief that the claimed compositions were a significant breakthrough in the field of cancer therapy.

For the reasons set forth above, Applicants believe that claims 2, 4, 16, 18, 21, 22 and 40 are unobvious over Li et al. in view of Restifo et al. Thus, Applicants respectfully request withdrawal of this rejection.

A credit card payment submitted via Form PTO-2038 in the amount of $3,040.00, representing $810.00 for the fee for a large entity under 37 C.F.R. § 1.17(e) and $2,230.00 for the fee for a large entity under 37 C.F.R. § 1.17(a)(5) and a Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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